HFA-305

DEC 15 2005

FREEDOM OF INFORMATION SUMMARY

Supplemental New Animal Drug Application

NADA 140-883

LEGEND Multi Dose (hyaluronate sodium)
Injectable Solution

LEGEND Multi Dose Injectable Solution is indicated for the treatment of joint dysfunction of the carpus or fetlock in horses due to non-infectious synovitis associated with equine osteoarthritis

Sponsored by:

Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201

2006-140-883

FOIS 10

1. GENERAL INFORMATION:

a. File Number:	NADA 140-883
b. Sponsor:	Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201 Drug Labeler Code: 000859
c. Established Name:	Hyaluronate sodium
d. Proprietary Name:	LEGEND Multi Dose Injectable Solution
e. Dosage Form:	Injectable Solution
f. How Supplied:	20 mL vials
g. How Dispensed:	Rx
h. Amount of Active Ingredients:	10 mg/mL
i. Route of Administration:	Intravenous
j. Species/Class:	Equine
k. Recommended Dosage:	4 mL (40 mg) injected intravenously. Treatment repeated at weekly intervals for a total of three treatments.
l. Pharmacological Category:	Anti-inflammatory
m. Indications:	LEGEND Multi Dose Injectable Solution is indicated for the treatment of joint dysfunction of the carpus or fetlock in horses due to non-infectious synovitis associated with equine osteoarthritis.

n. Effect of Supplement: Approval of the supplement will add a multiple-dose vial containing the preservative benzyl alcohol.

2. EFFECTIVENESS:

This supplemental NADA does not require re-evaluation of effectiveness data. The effectiveness of LEGEND Multi Dose is based upon the existing LEGEND single dose approval. Please refer to the original NADA 140-883 Freedom of Information (FOI) summary dated September 12, 1991.

3. TARGET ANIMAL SAFETY:

This supplemental NADA does not require re-evaluation of target animal safety data. The safety of LEGEND Multi Dose is based upon the existing LEGEND single dose approval. Please refer to the original NADA 140-883 Freedom of Information (FOI) summary dated September 12, 1991.

4. HUMAN SAFETY:

This drug is intended for use in horses, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this supplemental NADA. Human Warnings are provided on the product label as follows: "Do not use in horses intended for human consumption. Not for use in humans. Keep this and all other drugs out of the reach of children."

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that LEGEND Multi Dose when used under the labeled conditions of use is safe and effective for the treatment of joint dysfunction of the carpus or fetlock in horses due to non-infectious synovitis associated with equine osteoarthritis.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to make a diagnosis of equine osteoarthritis.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

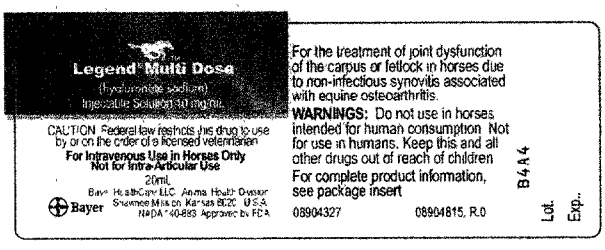
According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

LEGEND Multi Dose is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
4,808,576	April 28, 2006

6. *ATTACHMENTS:*

Facsimile labeling is attached as indicated below:
Vial Label – 20 mL vial
Carton Label – 20 mL vial
Package Insert


Legend® Multi Dose
(hyaluronate sodium)
Injectable Solution 10 mg/mL
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian
For Intravenous Use in Horses Only
Not for Intra-Articular Use
20mL
Bayer HealthCare LLC, Animal Health Division
Shawnee Mission, Kansas 66201 U.S.A.
NADA 140-885, Approved by FDA
Bayer
For the treatment of joint dysfunction of the carpus or fetlock in horses due to non-infectious synovitis associated with equine osteoarthritis.
WARNINGS: Do not use in horses intended for human consumption. Not for use in humans. Keep this and all other drugs out of reach of children.
For complete product information, see package insert
08904327
08904815, R.0
B4A4
Lot.
Exp..

Legend Multi Dose
Unit Carton

Legend® Multi Dose

(hyaluronate sodium)

Injectable Solution

For Intravenous Use in Horses Only
Not for Intra-Articular Use

CAUTION:
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
Legend® Multi Dose (hyaluronate sodium) Injectable Solution is a clear, colorless solution of low viscosity. Legend Multi Dose Injectable Solution is pyrogen free and sterile. It is administered by intravenous injection.

Hyaluronic acid, the conjugate acid of hyaluronate sodium, is extracted from the capsule of *Streptococcus* spp. and purified, resulting in a form which is essentially free of protein and nucleic acids.

Legend Multi Dose Injectable Solution is supplied in 20 mL vials. Each mL contains 10 mg hyaluronate sodium, 8.5 mg sodium chloride, 0.223 mg sodium phosphate dibasic, 0.04 mg sodium phosphate monobasic and 15.63 mg benzyl alcohol as a preservative. The pH is adjusted to between 6.5 and 8.0 with sodium hydroxide or hydrochloric acid.

CHEMISTRY:
Hyaluronic acid, a glycosaminoglycan, can exist in the following forms depending upon the chemical environment in which it is found: as the acid, hyaluronic acid; as the sodium salt, sodium hyaluronate (hyaluronate sodium); or as the hyaluronate anion. These terms may be used interchangeably but in all cases, reference is made to the glycosaminoglycan composed of repeating subunits of D-glucuronic acid and N-acetyl-D-glucosamine linked together by glycosidic bonds. Since this product originates from a microbial source, there is no potential for contamination with dermatan or chondroitin sulfate or any other glycosaminoglycan.

CLINICAL PHARMACOLOGY:
Hyaluronic acid is a naturally occurring substance present in connective tissue, skin, vitreous humour and the umbilical cord in all mammals. High concentrations of hyaluronic acid are also found in the synovial fluid. It also constitutes the major component of the capsule of certain microorganisms. The hyaluronic acid produced by bacteria is of the same structure and configuration as that found in mammals.

The actual mechanism of action for hyaluronate sodium in the healing of degenerative joint disease is not completely understood. One major function appears to be the regulation of normal cellular constituents. This effect decreases the impact of exudation, enzyme release and subsequent degradation of joint integrity. Additionally, hyaluronate sodium exerts an anti-inflammatory action by inhibiting the movement of granulocytes and macrophages.[1] Hyaluronate molecules are long chains which form a filter network interspersed with normal cellular fluids.

INDICATIONS:
Legend Multi Dose (hyaluronate sodium) Injectable Solution is indicated in the treatment of joint dysfunction of the carpus or fetlock in horses due to non-infectious synovitis associated with equine osteoarthritis.

DOSAGE AND ADMINISTRATION:
4 mL (40 mg) injected intravenously. Treatment may be repeated at weekly intervals for a total of three treatments.

Use aseptic technique and inject slowly into the jugular vein.

Horses should be given stall rest after treatment before gradually resuming normal activity.

CONTRAINDICATIONS:
There are no known contraindications for the use of Legend Multi Dose Injectable Solution in horses.

RESIDUE WARNING:
Do not use in horses intended for human consumption.

HUMAN WARNINGS:
Not for use in humans. Keep this and all other drugs out of reach of children.

ANIMAL SAFETY WARNINGS:
Not for intra-articular use. The intra-articular safety of hyaluronate sodium with benzyl alcohol has not been evaluated.

PRECAUTIONS:
Radiographic evaluation should be carried out in cases of acute lameness to ensure that the joint is free from serious fracture.

The safety of Legend Multi Dose Injectable Solution has not been evaluated in breeding stallions or in breeding, pregnant or lactating mares.

ADVERSE REACTIONS:
No local or systemic side effects were observed in the field studies using Legend Injectable Solution.

Post-Approval Experience: While all adverse reactions are not reported, the following adverse reactions are based on voluntary post-approval reporting for Legend Injectable Solution: Occasional depression, lethargy, and fever.

For medical emergencies or to report adverse reactions, call 1-800-422-9874.

EFFECTIVENESS:
Effectiveness studies utilizing Legend Multi Dose Injectable Solution were not performed. Legend Multi Dose Injectable Solution was approved based on the conclusion that the effectiveness of Legend Multi Dose Injectable Solution will not differ from that demonstrated for the original formulation of Legend Injectable Solution.

Twenty-one horses with lameness in either the carpal or fetlock joints were treated intravenously with Legend Injectable Solution in a well-controlled field study conducted at four locations. One, two or three injections were given based on clinical improvement. Overall clinical improvement was judged as excellent or good in 90% of the cases treated intravenously with Legend Injectable Solution.

ANIMAL SAFETY:
Animal safety studies utilizing Legend Multi Dose Injectable Solution were not performed. Legend Multi Dose Injectable Solution was approved based on the conclusion that the safety of Legend Multi Dose Injectable Solution will not differ from that demonstrated for the original formulation of Legend Injectable Solution.

Legend Injectable Solution was administered to normal horses at one, three and five times the recommended intravenous dosage of 40 mg. Treatments were given once weekly for nine consecutive weeks (three times the maximum duration). No systemic clinical signs were observed nor were there any adverse effects upon hematology or clinical chemistry parameters.

STORAGE:
Do not store above 40° C (104° F).

HOW SUPPLIED:
Legend Multi Dose Injectable Solution is supplied in 20 mL bottles.

REFERENCE:
[1]Swanstrom, O.G. 1978, Hyaluronate (hyaluronic acid) and its use, Proc. American Assoc. Equine Pract., 24th annual convention, pp. 345-348.

U.S. Patent No. 4,808,576

For customer service or to obtain product information, including a Material Safety Data Sheet, call 1-800-633-3796.

08904327 Made in U.S.A. September, 2005
08904793, R0 NADA 140-883, Approved by FDA

Bayer

Bayer HealthCare LLC
Animal Health Division
Shawnee Mission, Kansas 66201 U.S.A.

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